Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke

De Marchis, Gian Marco ; Schneider, Juliane ; Weck, Anja ; Fluri, Felix ; Fladt, Joachim ; Foerch, Christian ; Mueller, Beat ; Luft, Andreas ; Christ-Crain, Mirjam ; Arnold, Marcel ; Katan, Mira

Abstract: OBJECTIVE To validate midregional proatrial natriuretic peptide (MR-proANP) for outcome prediction and diagnosis of cardioembolic stroke etiology compared to established clinical variables. METHODS In this prospective multicenter cohort study, we quantified MR-proANP levels in ischemic stroke patients within 24 hours of onset. Primary outcome measures were 90-day mortality, unfavorable functional outcome (modified Rankin Scale score >2), and cardioembolic stroke etiology diagnosed during hospitalization. RESULTS Of 788 included patients, 783 completed their 90-day follow-up, and 118 patients (15%) died. After full adjustment, MR-proANP levels were associated with 90-day mortality (adjusted hazard ratio 6.12, 95% confidence interval [CI] 2.36-15.84, = 0.01) and functional outcome (adjusted odds ratio [aOR] 2.46, 95% CI 1.05-5.74, = 0.038). For mortality prediction, adding MR-proANP to the regression model increased its discriminatory accuracy, and the continuous net reclassification index (cNRI) was 49% (95% CI 26%-78%, < 0.001). For functional outcome, there was no significant improvement in discrimination or reclassification. Cardioembolic stroke etiology and the diagnosis of atrial fibrillation at hospital discharge were associated with MR-proANP with an aOR of 2.10 (95% CI 1.11-3.97, = 0.02) and 18.35 (95% CI 7.94-42.45, < 0.001), respectively. The cNRI of MR-proANP for cardioembolic stroke etiology was not significant, as opposed to atrial fibrillation (78%, 95% CI 60%-89%, < 0.001). MR-proANP levels 289 pmol/L had a specificity of 86% and sensitivity of 48% for the diagnosis of atrial fibrillation. CONCLUSION MR-proANP is a newly validated blood biomarker providing additional prognostic information for mortality after stroke. Higher MR-proANP levels were associated with cardioembolic stroke etiology and, even more strongly, atrial fibrillation.

DOI: https://doi.org/10.1212/WNL.0000000000004922

ARTICLE

Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke

Gian Marco De Marchis, MD, MS,* Juliane Schneider, MD,* Anja Weck, MD, Felix Fluri, MD, Joachim Fladt, MD, Christian Foerch, MD, Beat Mueller, MD, Andreas Luft, MD, Mirjam Christ-Crain, MD, PhD, Marcel Arnold, MD,* and Mira Katan, MD, MS*

Correspondence
Dr. Katan
Mira.katan@usz.ch

Neurology® 2018;90:e455-e465. doi:10.1212/WNL.0000000000004922

Abstract

Objective

To validate midregional proatrial natriuretic peptide (MR-proANP) for outcome prediction and diagnosis of cardioembolic stroke etiology compared to established clinical variables.

Methods

In this prospective multicenter cohort study, we quantified MR-proANP levels in ischemic stroke patients within 24 hours of onset. Primary outcome measures were 90-day mortality, unfavorable functional outcome (modified Rankin Scale score >2), and cardioembolic stroke etiology diagnosed during hospitalization.

Results

Of 788 included patients, 783 completed their 90-day follow-up, and 118 patients (15%) died. After full adjustment, MR-proANP levels were associated with 90-day mortality (adjusted hazard ratio 6.12, 95% confidence interval [CI] 2.36–15.84, $p = 0.01$) and functional outcome (adjusted odds ratio [aOR] 2.46, 95% CI 1.05–5.74, $p = 0.038$). For mortality prediction, adding MR-proANP to the regression model increased its discriminatory accuracy, and the continuous net reclassification index (cNRI) was 49% (95% CI 26%–78%, $p < 0.001$). For functional outcome, there was no significant improvement in discrimination or reclassification. Cardioembolic stroke etiology and the diagnosis of atrial fibrillation at hospital discharge were associated with MR-proANP with an aOR of 2.10 (95% CI 1.11–3.97, $p = 0.02$) and 18.35 (95% CI 7.94–42.45, $p < 0.001$), respectively. The cNRI of MR-proANP for cardioembolic stroke etiology was not significant, as opposed to atrial fibrillation (78%, 95% CI 60%–89%, $p < 0.001$). MR-proANP levels ≥289 pmol/L had a specificity of 86% and sensitivity of 48% for the diagnosis of atrial fibrillation.

Conclusion

MR-proANP is a newly validated blood biomarker providing additional prognostic information for mortality after stroke. Higher MR-proANP levels were associated with cardioembolic stroke etiology and, even more strongly, atrial fibrillation.

*These authors contributed equally to this work.

From the Department of Neurology and Stroke Center (G.M.D.M., J.F.) and Department of Endocrinology (M.C.-C.), University Hospital Basel; Department of Neurology (J.S., A.L., M. K.), University Hospital of Zurich; Department of Neurology and Neuroradiology (A.W., M.A.), Inselspital University of Berne, Switzerland; Department of Neurology (F.F.), University Hospital of Würzburg; Department of Neurology (C.F.), Goethe University, Frankfurt, Germany; and Medical University Department (B.M.), Kantonsspital Aarau, Switzerland.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AUC = area under the ROC curve; **BNP** = brain natriuretic peptide; **CI** = confidence interval; **CoRisk** = Copeptin for Risk Stratification in Acute Stroke Patients; **DWI** = diffusion-weighted imaging; **eGFR** = estimated glomerular filtration rate; **IQR** = interquartile range; **MR-proANP** = midregional proatrial natriuretic peptide; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NRI** = net reclassification index; **NT-proBNP** = N-terminal probrain natriuretic peptide; **OR** = odds ratio; **ROC** = receiver operating characteristic; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Blood markers measured immediately after an acute ischemic stroke may represent important adjuncts to traditional risk factors in the emergency setting. Tailoring treatment based on reliably estimated risk may improve patient outcome.

In routine clinical practice, blood biomarkers can be useful if they improve the prognostic accuracy of established clinical variables such as age and stroke severity.[1,2] However, before biomarkers are implemented in clinical practice, validation is crucial, as shown by a meta-analysis suggesting that pilot studies on blood biomarkers typically report higher effect sizes than subsequent larger validation studies of the same blood marker.[3]

Previous monocentric studies have shown that midregional proatrial natriuretic peptide (MR-proANP) is a promising prognostic and diagnostic biomarker among patients with acute ischemic stroke. In particular, MR-proANP improved the discriminatory ability of the NIH Stroke Scale (NIHSS) score[4] for 90-day mortality.[5] Through an independent, multicenter prospective cohort study, we aimed to validate the accuracy of MR-proANP in predicting functional outcome and mortality compared to established clinical variables. Moreover, this study sought to evaluate the accuracy of MR-proANP for identifying cardioembolic stroke and atrial fibrillation.

Methods

Standard protocol approvals, registrations, and patient consents

This study (Copeptin for Risk Stratification in Acute Stroke Patients [CoRisk] study; clinicaltrials.gov, NCT00878813) was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the local ethics committees. All patients or their welfare guardians provided written informed consent for the collection of data, blood samples, and subsequent analyses.

Study design and cohort description

The methodology of this multicenter cohort study has been published previously.[6] Briefly, the primary endpoint included disability (modified Rankin Scale [mRS] score 3–5) and mortality (mRS score 6) at 90 days after stroke. We included patients >18 years of age with an acute ischemic stroke within 24 hours of symptom onset admitted consecutively to the emergency department of each tertiary care center between March 24, 2009, and April 8, 2011. None of the patients enrolled in this study were part of a previous cohort evaluating MR-proANP.[5] We defined acute ischemic stroke according to the World Health Organization criteria as an acute focal neurologic deficit lasting >24 hours with no sign of acute intracranial bleeding on cerebral imaging.[7] Neither MRI nor a lesion on diffusion-weighted imaging (DWI) was mandatory for the diagnosis of stroke.

Exclusion criteria were missing informed consent; TIAs (duration ≤24 hours) regardless of DWI lesions, as prespecified in the published protocol[8]; and any other diagnosis different from ischemic stroke. Vascular neurologists prospectively recorded the NIHSS score on admission. CT or MRI was performed in each patient. MR-DWI was available for 537 stroke patients (68.5%). DWI lesion volumes were measured by experienced raters unaware of the clinical and laboratory findings. The lesion size was calculated by a commonly used semiquantitative method as previously described.[9] Lesions were categorized into 3 size classes: small lesion with a volume of <10 cm^3, medium lesion with a volume of 10 to 100 cm^3, or large lesion with a volume >100 cm^3.[10] Demographic and vascular risk factors were collected on admission. Moreover, comorbidities were assessed on admission by the modified Charlson Comorbidity Index.[11] Data on cardiac and neurovascular ultrasound and 24-hour ECGs were gathered to define stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[12]

Biomarker measurement

Blood was drawn in the emergency room within 24 hours of symptom onset. Samples were immediately centrifuged, divided into aliquots, and frozen at −80°C until the time of analysis. MR-proANP levels were assessed in plasma in a blinded batch analysis with the automated B·R·A·H·M·S KRYPTOR immunoassay technology (BRAHMS GmbH, Hennigsdorf, Germany). The lower detection limit was 2.1 pmol/L, and the functional assay sensitivity was <10 pmol/L (<20% interassay coefficient of variation, defined as the ratio of the SD to the mean). Median MR-proANP levels in healthy controls were reported to be 46.1 pmol/L and the 97.5 percentile was at 85.2 pmol/L.[13]

Follow-up and outcome measures

Three months after stroke, vascular neurologists and trained study nurses blinded to MR-proANP levels assessed outcome either during an outpatient visit or with a structured telephone interview. Unfavorable outcome was defined as an mRS score of 3 to 6 points. If patients died within the follow-up period, the date of death was recorded. Cardioembolic stroke was defined according to the TOAST classification. Furthermore, atrial fibrillation, as outcome variable, was defined as diagnosis of atrial fibrillation at hospital discharge, thus encompassing history of atrial fibrillation on admission and newly diagnosed atrial fibrillation during hospitalization.

Statistical analysis

Discrete variables were expressed as counts (percentages) and continuous variables as medians (interquartile range [IQR]). Biomarker data were log-transformed to achieve normality. The Shapiro-Wilk test was used to test for normality. Frequency comparisons for categorical baseline measurements were performed by the Fisher exact test. Two-group comparison of continuous, not normally distributed baseline data was performed by the Mann-Whitney *U* test. We used the Bonferroni method to correct *p* values for multiple univariate comparisons; i.e., we multiplied the uncorrected *p* values by the number of comparisons. To investigate the association of MR-proANP with functional outcome, cardioembolic etiology, and atrial fibrillation, we calculated logistic regression models, and for the association with mortality, we computed Cox regression models. To illustrate the mortality rate, patients were stratified by quartiles of MR-proANP levels, and Kaplan-Meier curves were computed and compared with the log-rank test. Odds ratios (ORs), hazard ratios, and 95% confidence intervals (CIs) were calculated, unadjusted and adjusted for demographic and vascular risk factors. As covariates for the multivariate models, we selected all the variables with a univariate $p < 0.01$ and, regardless of the *p* value, thrombolysis, heart failure, and cardioembolic stroke for the models concerning functional outcome and mortality. For cardioembolic stroke and atrial fibrillation as outcome, all the variables with a univariate $p < 0.01$ were included. Coronary heart disease was not included in any model because of collinearity with atrial fibrillation.

Interaction analyses were performed to investigate whether the predictive value of MR-proANP is modified by sex, age, stroke severity (NIHSS scores 0–6, 7–15, and >15), hypertension, diabetes mellitus, atrial fibrillation, heart failure, and estimated glomerular filtration rate (eGFR), categorized to represent relevant renal disease (cutoff <60 mL/min/1.73 m^2). The calibration of the logistic and Cox models was assessed with the Hosmer-Lemeshow goodness-of-fit test and Groennesby and Borgan test, respectively.

Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) as an overall discriminatory measure were calculated. The De Long test was used to compare the AUCs of 2 different single variables, whereas the likelihood ratio test was used to compare the AUCs of nested vs whole models. The whole model included all predictors that remained significant in the multivariate model ($p < 0.05$). In addition, we calculated cutoff ranges of MR-proANP (from 95% sensitivity to 95% specificity) for the main outcome measures (i.e., functional outcome, mortality, cardioembolic stroke, and atrial fibrillation).

To further estimate the additive benefit of MR-proANP levels to the traditional outcome predictor, we calculated the net reclassification index (NRI) on the basis of the model including predictors that remained significant in the multivariate model ($p < 0.05$). The NRI has been proposed to evaluate prognostic biomarkers.[2,14] To corroborate the findings, the change in the (pseudo) R^2 value (McFadden adjusted) of the regression model was determined by calculating a multivariate logistic regression model with and without MR-proANP as a regressor for functional outcome, mortality, and cardioembolic stroke. Statistics were calculated with Stata Statistical Software, release 14.2 (StataCorp LP, College Station, TX, 2015). Testing was 2 tailed, and values of $p < 0.05$ were considered statistically significant.

Results

Baseline data

From March 24, 2009, through April 8, 2011, a total of 788 patients with an acute ischemic stroke were consecutively included in the study. Overall, 783 patients completed their 90-day follow-up (follow-up rate 99.4%). The median age of the cohort was 71 (IQR 61–80) years, and 298 (38%) were women. Patient characteristics stratified by functional outcome and mortality are summarized in table 1. In addition, patient characteristics are summarized by tertiles of MR-proANP (table e-1, http://links.lww.com/WNL/A111).

Prediction of functional outcome after 3 months

At 90 days, 300 patients (38.3%) had an unfavorable outcome (mRS score 3–6). Median MR-proANP concentration was almost twice as high in patients with unfavorable than in those with favorable outcomes (225 [IQR 126–359] vs 127 [IQR 79–224] pmol/L, $p < 0.001$) (table 1 and figure e-1, http://links.lww.com/WNL/A110). In the multivariate logistic regression model, MR-proANP levels were associated with an unfavorable outcome (adjusted OR 2.46 for any 10-fold increase of MR-proANP, 95% CI 1.05–5.74, $p = 0.038$). Additional predictors of unfavorable outcome were age, stroke severity, eGFR, and large lesion size on DWI, and after adjustment for cardioembolic stroke and heart failure, MR-proANP remained associated with functional outcome (table 2). The multivariate models were well calibrated according to the goodness-of-fit test (Hosmer-Lemeshow $p = 0.4$). No significant interactions were found across subgroups for the prediction of functional outcome.

MR-proANP improved only marginally the discriminatory accuracy of the NIHSS and the whole multiple logistic regression model (AUC change from 0.85 [95% CI 0.83–0.88] to 0.86 [95% CI 0.83–0.88], $p < 0.0071$) (table 3 and figure e-2, http://links.lww.com/WNL/A110). An MR-proANP level of 112 pmol/L had a sensitivity of 81% and a specificity of 45% for functional

Table 1 Patient characteristics

		Functional outcome at 90 d				Mortality at 90 d			
	Total	Favorable outcome (mRS score 0–2)	Unfavorable outcome (mRS score 3–6)	*p* Value	Bonferroni *p* value	Alive	Dead	*p* Value	Bonferroni *p* value
No. (%)	783 (100)	483 (62)	300 (38)			665 (85)	118 (15)		
Demographic data									
Age, median (IQR), y	71 (61–80)	66 (58–76)	77 (68–83)	<0.001	<0.03	69 (59–78)	79 (71–85)	<0.0001	<0.003
Female sex, n (%)	298 (38)	162 (34)	136 (45)	0.001	0.03	247 (37)	51 (43)	0.22	1.0
Medical history, n (%)[a]									
Hypertension	539 (69)	312 (65)	227 (76)	0.001	0.03	446 (67)	93 (79)	0.013	0.38
Atrial fibrillation	153 (20)	77 (16)	76 (25)	0.002	0.06	117 (18)	36 (31)	0.005	0.15
Smoking history	138 (18)	98 (20)	40 (13)	0.01	0.29	125 (19)	13 (11)	0.024	0.70
Diabetes mellitus	125 (16)	59 (12)	66 (22)	<0.001	<0.03	94 (14)	31 (26)	0.003	0.09
Coronary heart disease	149 (19)	75 (16)	74 (25)	0.002	0.06	113 (17)	36 (31)	0.003	0.09
Dyslipidemia[b]	432 (55)	280 (58)	152 (51)	0.001	0.03	381 (57)	51 (43)	0.007	0.20
Heart failure	78 (10)	38 (8)	40 (13)	0.014	0.40	57 (9)	21 (18)	0.004	0.17
Previous cerebrovascular event	152 (19)	86 (18)	66 (22)	0.16	1.0	129 (19)	23 (19)	1.0	1.0
Modified Charlson Index, median (IQR)	0 (0–1)	0 (0–1)	1 (0–2)	<0.001	<0.03	0 (0–1)	1 (0–3)	<0.0001	<0.003
NIHSS score at admission, median (IQR)	6 (3–13)	4 (2–7)	13 (7–17.5)	<0.001	<0.03	5 (2–10)	15 (9–19)	<0.001	<0.03
Laboratory values, median (IQR)									
MR-proANP, pmol/L	159 (91–284)	127 (79–224)	225 (126–359)	<0.001	<0.03	139 (85–253)	262 (192–420)	0.0008	0.02
Glucose, mmol/L	6.3 (5.5–7.5)	6.0 (5.4–7.2)	6.7 (5.8–8.3)	<0.001	<0.03	6.2 (5.5–7.5)	6.7 (5.8–8.5)	0.0011	0.03
C-reactive protein, mg/L	3 (3–6)	3 (3–5)	3 (3–9)	<0.001	<0.03	3 (3–5)	4 (3–12)	<0.0001	<0.003
eGFR, mL/min/1.73 m^2	75 (61–92)	78 (65–93)	70 (55–90)	<0.001	<0.03	77 (63–92)	62 (52–84)	<0.001	<0.03
Lesion size on MR, DWI, n (%)[a],c									
None detected	39 (7)	32 (9)	7 (4)	0.074	1.0	38 (8)	1 (2)	0.16	1.0
Small (1–10 cm^3)	233 (43)	197 (53)	36 (22)	<0.001	<0.03	226 (47)	7 (14)	<0.001	<0.03
Medium (10–100 cm^3)	205 (38)	128 (35)	77 (46)	0.01	0.29	182 (38)	23 (45)	0.29	1.0

Continued

Table 1 Patient characteristics *(continued)*

		Functional outcome at 90 d				Mortality at 90 d			
	Total	Favorable outcome (mRS score 0–2)	Unfavorable outcome (mRS score 3–6)	*p* Value	Bonferroni *p* value	Alive	Dead	*p* Value	Bonferroni *p* value
Large (<100 cm^3)	60 (11)	14 (4)	46 (28)	<0.001	<0.03	40 (8)	20 (39)	<0.001	<0.03
Stroke etiology (TOAST), n (%)[a]									
Large vessel disease	109 (14)	64 (13)	45 (15)	0.46	1.0	99 (15)	10 (8)	0.06	1.0
Cardioembolic stroke	314 (40)	186 (39)	128 (43)	0.29	1.0	266 (40)	48 (41)	0.76	1.0
Small artery disease	45 (6)	40 (8)	5 (2)	<0.001	<0.03	43 (7)	2 (2)	0.05	1.0
Other known	28 (4)	16 (3)	12 (4)	0.85	1.0	27 (4)	1 (1)	0.12	1.0
Unknown	216 (28)	124 (26)	92 (31)	0.14	1.0	169 (25)	47 (40)	<0.004	0.12
Multiple causes	70 (9)	52 (11)	18 (6)	0.028	0.81	61 (9)	10 (8)	1.0	1.0
Treatment, n (%)[a]									
IV thrombolysis	160 (20)	97 (20)	63 (21)	0.76	1.0	136 (21)	24 (20)	0.98	1.0
IA thrombolysis	124 (16)	47 (10)	77 (26)	0.001	0.03	93 (14)	31 (26)	0.0008	0.02
IV and IA thrombolysis	35 (4)	16 (3)	19 (6)	0.046	1.0	27 (4)	8 (7)	0.18	1.0

Abbreviations: DWI = diffusion-weighted imaging; eGFR = estimated glomerular filtration rate; IA = intra-arterial; IQR = interquartile range; MR = magnetic resonance; MR-proANP = midregional proatrial natriuretic peptide; mRS = modified Rankin scale; NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.
Statistics: values are median (IQR) or percent (number). The *p* values were assessed with the Mann-Whitney *U* test and Fisher exact test. Bonferroni *p* values <0.05 were considered statistically significant.
[a] Because of rounding, percentages may not total 100.
[b] Dyslipidemia: of 432 patients who had dyslipidemia, 183 took statins on admission.
[c] Percentages refer to patients for whom information on DWI lesion was present (n = 537).

Table 2 Multivariate logistic and Cox regression analyses for 90-day functional outcome and mortality WITH and WITHOUT MR-proANP

	With MR-proANP			Without MR-proAMP		
Predictors	**OR**	**95% CI**	***p* Value**	**OR**	**95% CI**	***p* Value**
Functional outcome						
MR-proANP[a]	2.46	1.05–5.74	0.038	NA	NA	NA
Age	1.06	1.04–1.08	<0.001	1.07	1.05–1.09	<0.001
Female sex	1.19	0.78–1.82	0.41	1.18	0.78–1.80	0.44
Hypertension	0.91	0.56–1.48	0.71	0.94	0.58–1.51	0.79
History of atrial fibrillation	1.02	0.56–1.88	0.95	1.14	0.62–2.07	0.68
Diabetes mellitus	1.42	0.77–2.62	0.26	1.36	0.74–2.50	0.32
Heart failure	1.08	0.53–2.17	0.84	1.13	0.56–2.30	0.73
Modified Charlson Index	1.10	0.92–1.32	0.31	1.13	0.94–1.35	0.19
NIHSS score at admission	1.21	1.16–1.27	<0.001	1.22	1.17–1.27	<0.001
Glucose[a]	1.30	0.21–7.99	0.78	1.38	0.23–8.34	0.73
C-reactive protein[a]	1.64	0.98–2.76	0.060	1.69	1.00–2.83	0.05
eGFR[a]	2.16	1.16–4.02	0.016	1.70	0.95–3.03	0.072
Large lesion size on MR, DWI (<100 cm^3)	3.61	1.47–8.90	0.005	3.68	1.51–9.01	0.004
Cardioembolic stroke	0.75	0.43–1.32	0.32	0.79	0.45–1.38	0.41
Small artery disease stroke	0.47	0.16–1.42	0.18	0.43	0.14–1.29	0.13
IV thrombolysis	0.59	0.34–1.03	0.06	0.58	0.33–1.01	0.05
IA thrombolysis	0.63	0.34–1.03	0.17	0.64	0.33–1.25	0.19
IV and IA thrombolysis	0.72	0.27–1.87	0.49	0.70	0.27–1.82	0.47
Pseudo-R^2			0.3292			
Pseudo-R^2 without MR-proANP						0.3245

	With MR-proANP			Without MR-proAMP		
Predictors	**Hazard ratio**	**95% CI**	***p* Value**	**Hazard ratio**	**95% CI**	***p* Value**
Mortality						
MR-proANP[a]	6.12	2.36–15.84	0.01	NA	NA	NA
Age	1.03	1.01–1.05	0.014	1.04	1.02–1.06	<0.001
History of atrial fibrillation	1.18	0.67–2.07	0.57	1.35	0.77–2.38	0.30
Diabetes mellitus	2.27	1.31–3.96	0.004	2.11	1.22–3.65	0.008
Dyslipidemia	0.49	0.32–0.75	0.001	0.49	0.32–0.74	<0.001
Heart failure	1.08	0.92–1.18	0.83	1.14	0.55–2.33	0.73
Modified Charlson Index	1.04	0.96–1.18	0.53	1.05	0.93–1.19	0.43
NIHSS score at admission	1.10	1.07–1.13	<0.001	1.10	1.08–1.13	<0.001
C-reactive protein[a]	1.82	1.16–2.84	0.009	1.78	1.15–2.75	0.01
Glucose[a]	1.31	0.22–7.82	0.77	1.92	0.32–11.4	0.48
eGFR[a]	1.10	0.61–1.99	0.75	0.65	0.39–1.09	0.10
Small lesion size (1–10 cm^3)	0.34	0.14–0.80	0.013	0.30	0.13–0.71	0.006

Continued

Table 2 Multivariate logistic and Cox regression analyses for 90-day functional outcome and mortality WITH and WITHOUT MR-proANP *(continued)*

	With MR-proANP			Without MR-proAMP		
Predictors	**Hazard ratio**	**95% CI**	***p* Value**	**Hazard ratio**	**95% CI**	***p* Value**
Large lesion size (<100 cm^3)	1.21	0.66–2.22	0.54	1.19	0.65–2.18	0.57
Cardioembolic stroke	0.86	0.45–1.64	0.64	0.94	0.49–1.78	0.84
Undetermined stroke	2.62	1.43–4.80	0.002	2.26	1.26–4.08	0.007
IV thrombolysis	1.02	0.57–1.84	0.95	0.95	0.52–1.72	0.86
IA thrombolysis	0.74	0.42–1.30	0.30	0.77	0.44–1.34	0.35
IV and IA thrombolysis	1.87	0.79–4.39	0.15	1.06	0.67–3.83	0.28

Abbreviations: CI = confidence interval; DWI = diffusion-weighted imaging; eGFR = estimated glomerular filtration rate; IA = intra-arterial; MR = magnetic resonance; MR-proANP = midregional proatrial natriuretic peptide; NA = not applicable; NIHSS = NIH Stroke Scale; OR = odds ratio.
[a] ORs and hazard ratio refer to a 1-unit increase in the explanatory variable and to any 10-fold increase in MR-proANP, glucose, C-reactive protein, and eGFR (log transformed with a base of 10). All of the covariates entered in the models are listed in the table.

outcome within 3 months (table e-2, http://links.lww.com/WNL/A111). Accordingly, the combination of MR-proANP with the regression model led to a modest increase in the continuous NRI of 9% (95% CI −0.2% to 37%, $p = 0.62$) and categorical NRI of 1.4% (95% CI −2.4% to 5.0%, $p = 0.61$).

Prediction of death within 90 days after stroke

Within 90 days, 118 patients (15%) had died (table 1). MR-proANP levels were higher among patients who died compared to survivors (262 [IQR 192–420] vs 139 [IQR 85–253] pmol/L, $p < 0.001$) (figure e-3, http://links.lww.com/WNL/A110). The Kaplan-Meier survival curves of patients stratified per MR-proANP quartiles differed significantly ($p < 0.001$, log-rank test, figure e-4).

In the multivariate Cox regression model, MR-proANP was associated with 90-day mortality with a hazard ratio of 6.12 (95% CI 2.36–15.84, $p = 0.01$). Table 2 summarizes additional predictors of mortality, including heart failure and cardioembolic stroke etiology. The multivariate models were well calibrated

Table 3 ROC analyses of 90-day functional outcome and mortality

Predictors	**AUC**	**95% CI**	**De Long test[a]**	**Likelihood ratio test[b]**
Functional outcome				
MR-proANP	0.68	0.65–0.72	NA	NA
NIHSS score	0.82	0.78–0.85	0.01	NA
Combined score (NIHSS score and MR-proANP)	0.83	0.80–0.86	0.07	<0.001
Model 1[c]	0.85	0.83–0.88	NA	NA
Model 1 and MR-proANP[c]	0.86	0.83–0.88	0.60	<0.0071
Mortality				
MR-proANP	0.73	0.68–0.78	NA	NA
NIHSS score	0.80	0.77–0.84	0.01	NA
Combined score (NIHSS score and MR-proANP)	0.84	0.80–0.87	0.02	<0.01
Model 2[d]	0.87	0.84–0.90	NA	NA
Model 2 and MR-proANP[d]	0.89	0.85–0.92	0.03	<0.001

Abbreviations: AUC = area under the ROC curve; CI = confidence interval; MR-proANP = midregional proatrial natriuretic peptide; NA = not applicable; NIHSS = NIH Stroke Scale; ROC = receiver operating characteristics.
[a] To compare the AUCs of 2 different single variables, the De Long test was used.
[b] To compare the AUCs of nested vs whole models, the likelihood ratio test was used.
[c] Model 1 (age, NIHSS score, large lesion size, estimated glomerular filtration rate, cardioembolic stroke, IV thrombolysis, intra-arterial thrombolysis, IV/intra-arterial thrombolysis, heart failure), multivariate logistic regression model, is presented in table 2 (top).
[d] Model 2 (age, dyslipidemia, C-reactive protein, diabetes mellitus, NIHSS score, small lesions size, unclear stroke, cardioembolic stroke, IV thrombolysis, intra-arterial thrombolysis, IV/intra-arterial thrombolysis, heart failure), Cox regression model, is presented in table 2 (bottom).

Table 4 Baseline characteristics stratified by cardioembolic stroke

	Total	No cardioembolic stroke	Cardioembolic stroke	*p* Value	Bonferroni *p* value
No. (%)	783 (100)	469 (60)	314 (40)		
Demographic data					
Age, median (IQR), y	71 (61–80)	70 (59–79)	73 (62–81)	0.017	0.34
Women, n (%)[a]	298 (38)	160 (34)	138 (44)	0.007	0.14
Medical history, n (%)[a]					
Hypertension	539 (69)	311 (66)	228 (73)	0.07	1.0
Atrial fibrillation	153 (20)	18 (4)	135 (43)	<0.001	<0.02
Smoking	138 (18)	98 (21)	40 (13)	0.007	0.14
Diabetes mellitus	125 (16)	81 (17)	44 (14)	0.19	1.0
Coronary heart disease	149 (19)	17 (4)	132 (44)	<0.001	<0.02
Heart failure	78 (10)	30 (6)	48 (15)	<0.001	<0.02
Dyslipidemia	432 (55)	282 (60)	150 (48)	0.002	0.04
Previous cerebrovascular event	152 (19)	96 (21)	56 (18)	0.41	1.0
Clinical data, median (IQR)					
NIHSS score at admission	6 (3–13)	6 (3–12)	6.5 (3–14.5)	0.11	1.0
Modified Charlson Index	0 (0–1)	0 (0–1)	1 (0–1)	0.36	1.0
Laboratory values, median (IQR)					
MR-proANP, pmol/L	159 (91–284)	128 (84–216)	233 (116–359)	<0.001	<0.02
Glucose, mmol/L	6.3 (5.5–7.5)	6.3 (5.6–7.5)	6.2 (5.4–7.6)	0.25	1.0
C-reactive Protein, mg/L	3 (3–6)	3 (3–5)	3 (3–7)	0.17	1.0
eGFR, mL/min/1.73 m^2	75 (61–92)	76 (63–93)	73 (58–90)	0.03	0.6
Lesion size on MR, DWI, n (%)[a,b]					
None detected	39 (7)	29 (9)	10 (5)	0.17	1.0
Small (1–10 cm^3)	233 (43)	158 (46)	75 (39)	0.09	1.0
Medium (10–100 cm^3)	205 (38)	117 (34)	88 (45)	0.013	0.26
Large (<100 cm^3)	60 (11)	38 (11)	22 (11)	1.00	1.0

Abbreviations: DWI = Diffusion weighted imaging; eGFR = estimated glomerular filtration rate; IQR = interquartile range; MR = magnetic resonance; MR-proANP = midregional proatrial natriuretic peptide; NIHSS = NIH Stroke Scale.
Statistics: values are median (IQR) or percent (number). The *p* values were assessed with the Mann-Whitney *U* test and Fisher exact test. Bonferroni *p* values <0.05 were considered statistically significant.
[a] Because of rounding, percentages may not total 100.
[b] Percentages refer to patients for whom information on DWI lesion was present (n = 537).

according to the goodness-of-fit test [Groennesby and Borgan test $\chi^2(1) = 1.4$; $p = 0.2$]. No significant interactions were found across different subgroups for the prediction of mortality.

The overall discriminative ability of MR-proANP to distinguish survivors from nonsurvivors, assessed with the AUC, was 0.73 (95% CI 0.68–0.78). When MR-proANP was combined with the Cox regression model, the discriminatory accuracy increased from an AUC of 0.87 (95% CI 0.84–0.90) to 0.89 (95% CI 0.85–0.92, $p < 0.001$) (table 3 and figures e-5 and e-6, http://links.lww.com/WNL/A110). An MR-proANP level of 163 pmol/L had a sensitivity of 81% and a specificity of 56% for death within 3 months (table e-2, http://links.lww.com/WNL/A111).

The combination of MR-proANP with the Cox regression model led to a continuous NRI of 49% (95% CI 26%–78%, $p < 0.001$) and categorical NRI of 16% (95% CI 9.5%–29.0%, $p < 0.001$).

Identification of cardioembolic stroke and atrial fibrillation

Median MR-proANP levels were almost twice as high in patients with cardioembolic stroke compared to other stroke

Table 5 Multivariate logistic regression analyses for cardioembolic stroke WITH and WITHOUT MR-proANP

	With MR-proANP			Without MR-proAMP		
Predictors	**OR**	**95% CI**	***p* Value**	**OR**	**95% CI**	***p* Value**
MR-proANP, pmol/L[a]	2.10	1.11–3.97	0.023	NA	NA	NA
Age	0.98	0.97–1.00	0.023	0.99	0.97–1.00	0.14
Female sex	1.35	0.95–1.91	0.09	1.43	1.01–2.02	0.041
History of atrial fibrillation	15.34	8.87–26.53	<0.001	17.44	10.2–29.9	<0.001
Smoking	0.80	0.51–1.27	0.35	0.77	0.48–1.21	0.27
Dyslipidemia	0.70	0.51–1.27	0.35	0.69	0.50–0.97	0.035
Heart failure	1.78	0.99–3.18	0.053	2.07	1.18–3.66	0.012
Pseudo-R^2			0.2016			
Pseudo-R^2 without MR-proANP						0.1964

Abbreviations: CI = confidence interval; MR-proANP = midregional proatrial natriuretic peptide; NA = not applicable; OR = odds ratio.
[a] OR refers to a 1-unit increase in the explanatory variable and to any 10-fold increase in MR-proANP (log transformed with a base of 10). All of the covariates entered in the model are listed in the table.

etiologies (tables 4 and 5). In the multivariate logistic model, MR-proANP was associated with cardioembolic stroke (OR 2.10, 95% CI 1.11–3.97, $p = 0.023$). The multivariate models were well calibrated ($p = 0.7$).

MR-proANP levels ≥255 pmol/L had a sensitivity of 44% and a specificity of 82% for a cardioembolic etiology (table e-2, http://links.lww.com/WNL/A111). Adding MR-proANP to the multivariate regression model increased the discriminatory accuracy for cardioembolic from an AUC of 0.74 (95% CI 0.71–0.78) to 0.76 (95% CI 0.72–0.80, $p = 0.002$) (table e-3). However, the combination of MR-proANP with the logistic regression model led to a nonsignificant continuous NRI of 20% (95% CI 4.9%–4.6%, $p = 0.43$) and a categorical NRI of 6.3% (95% CI −5.7% to 21.4%, $p = 0.19$).

Among patients with diagnosis of atrial fibrillation at hospital discharge, MR-proANP levels were more than twice as high as in patients without atrial fibrillation (table e-4, http://links.lww.com/WNL/A111). In the multivariate model, MR-proANP was independently associated with diagnosis of atrial fibrillation at hospital discharge (OR 18.35, 95% CI 7.94–42.45, $p < 0.001$) (table e-5). MR-proANP levels ≥289 pmol/L had a specificity of 86% and a sensitivity of 48% for the diagnosis of atrial fibrillation at hospital discharge (table e-2). Adding MR-proANP to significant predictors of atrial fibrillation increased the AUC from 0.70 (95% CI 0.67–0.74) to 0.79 (95% CI 0.76–0.82, $p < 0.001$) (table e-6), leading to a continuous NRI of 78% (95% CI 60%–89%, $p < 0.001$) and a categorical NRI of 39% (95% CI 27%–55%, $p < 0.001$).

Discussion

In this prospective multicenter cohort of acute ischemic stroke patients, MR-proANP was an independent predictor of functional outcome, mortality, cardioembolic stroke etiology, and atrial fibrillation. Of note, across the analyzed subgroups, the association between MR-proANP and the outcome variables remained significant. When MR-proANP was added to prognostic models using different statistical methods (i.e., comparison of AUCs, NRI, and change in pseudo-R^2), we found an improvement for mortality and the identification of atrial fibrillation. Our multicenter study confirms and extends the conclusions of a previous single-center cohort study of 362 patients with acute ischemic stroke, which also found an independent association between MR-proANP and mortality, as well as cardioembolic stroke.[5] Because of the larger sample size of the current study, it was possible to adjust for several prognostic factors, to compare subgroups, and to assess the incremental value of MR-proANP beyond the most important demographic and vascular risk factors.

In stroke research, brain natriuretic peptide (BNP) has been shown to predict all-cause mortality and, in some studies, functional outcome.[5,15] In a meta-analysis of 3,498 patients with ischemic stroke, BNP and N-terminal probrain natriuretic peptide (NT-proBNP) added information to clinical predictors (NIHSS score, age, sex) for the prediction of mortality (NRI 8.1%) but not for functional outcome,[16] which is in line with our observation that MR-proANP had a better prognostic accuracy for mortality rather than functional outcome. The pathophysiologic relationship between elevated levels of natriuretic peptides and stroke prognosis is still unclear. The highest ANP levels within the CNS are found in the hypothalamus and septum.[17] Activation of the hypothalamus-pituitary-adrenal axis is associated with elevated levels of natriuretic peptides. High cortisol, copeptin, and natriuretic peptide values predict long-term mortality after ischemic stroke, suggesting that a neurohumoral disturbance is linked to unfavorable outcome.[5,18] In addition, ANP is secreted by

atrial myocytes in response to different stimuli such as atrial distension, angiotensin II stimulation, endothelin, and sympathetic stimulation.[19,20] The prohormone of ANP, known as MR-proANP, has a longer half-life and makes serum measurements more feasible.[21]

For the diagnosis of acute heart failure, MR-proANP has been shown to be noninferior to BNP and seemed to improve the diagnostic accuracy of BNP levels between 100 and 500 pg/mL.[22] In chronic heart failure, with regard to mortality, MR-proANP outperformed BNP and NT-proBNP. The proportion of explained variance (4.36%) showed that MR-proANP was a significantly stronger predictor of death than either NT-proBNP (2.47%, $p < 0.0001$) or BNP (2.42%, $p < 0.0001$). Both the high biological stability of MR-proANP and a new assay technology are potential explanations for these findings.[23]

The independent association of natriuretic peptides with cardioembolic stroke (after adjustment for age and evident atrial fibrillation) could be explained through an underlying atrial cardiopathy, which can presumably anticipate even atrial fibrillation.[24] Thus, ANP may be a potential blood marker of atrial cardiopathy, which is also associated with cardioembolic stroke.[24] There may even be a causal relationship of ANP with the development of atrial fibrillation because individuals with familial atrial fibrillation demonstrate a frameshift mutation in the gene encoding ANP.[25] Because up to 30% of patients with cryptogenic stroke may have undetected paroxysmal atrial fibrillation or other unrecognized cardioembolic sources,[26] MR-proANP levels might help identify patients who will benefit from prolonged cardiac rhythm monitoring or oral anticoagulants for recurrence prophylaxis. However, among patients with strokes initially considered cryptogenic, additional studies are needed to assess the association of MR-proANP with paroxysmal atrial fibrillation and cardioembolism.

This study has limitations. First, the study is lacking a direct comparison of MR-proANP with other natriuretic peptides. Second, the proportion of patients with cardioembolic stroke was somewhat higher compared to other epidemiologic studies. Possible explanations include referral bias, because patients with cardioembolic stroke tend to have more severe strokes and be referred to tertiary care centers like the ones participating in this study, and a higher detection rate of cardioembolic sources due to extensive cardiac workup (almost half of the patients underwent transesophageal echocardiography). Third, no follow-up data on the detection of atrial fibrillation after hospitalization were available, leaving the question of whether MR-proANP would help reclassify cryptogenic into cardioembolic stroke. Fourth, some baseline variables were missing, including the proportion of patients with anterior vs posterior circulation and the frequency of large vessel occlusion, which may contribute to outcome prediction. Fifth, MR-proANP was associated not only with mortality but also with other factors such as age, NIHSS score, infarct size, hypertension, and diabetes mellitus, which were adjusted for with a Cox regression model. However, residual confounding effects cannot be excluded. Finally, the interrater agreement of the 2 raters of DWI lesion volumes was not available.

In the emergency setting, MR-proANP can improve the risk stratification for 90-day mortality after stroke. Higher MR-proANP levels were also associated with cardioembolic stroke etiology and, even more strongly, atrial fibrillation. In the future, MR-proANP may facilitate the selection of patients who will benefit from prolonged cardiac rhythm monitoring and anticoagulation.

Author contributions

Study concept and design: De Marchis, Katan, Arnold, Christ-Crain, Mueller. Acquisition of data: De Marchis, Weck, Fluri, Foerch. Statistical analysis: Schneider, De Marchis, Katan. Drafting of the manuscript: Schneider, De Marchis, Katan. Critical revision of the manuscript for important intellectual content: all authors. Obtained funding: Katan, De Marchis, Arnold. Administrative, technical, or material support: De Marchis. Study supervision: Katan, De Marchis.

Study funding

Supported by Swiss National Science Foundation (PZ00P3_142422 to MK); De Quervain research grant, Switzerland (to G.M.D.M.); Foundation of the Inselspital Bern (to G.M.D.M.); Foundation Pro Scientia et Arte, Bern (to G.M.D.M.); grant from the Foundation Jubiläumsstiftung der Schweizerischen Lebensversicherungs-und Rentenanstalt für Volksgesundheit und medizinische Forschung (to G.M.D.M.); and Transatlantic Career Development Grant from the Foundation Leducq (to M.K.). None of the supporting entities had a role in the collection, management, analysis, or interpretation of the data or the preparation or approval of the manuscript.

Disclosure

G. De Marchis received an unconditional research grant for the measurement of MR-proANP in the CoRisk study from BRAHMS GmbH, Hennigsdorf, Germany. The sponsor had no role in the collection, management, analysis, or interpretation of the data or the preparation or approval of the manuscript. J. Schneider, A. Weck, F. Fluri, J. Fladt, C. Foerch, and B. Mueller report no disclosures relevant to the manuscript. A. Luft reports consultancies at Bayer Scientific Advisory Board, Boehringer Ingelheim Scientific Advisory Board, Hocoma AG Volketswil Scientific Advisory Board, and consultancy/lectures at AMGEN Scientific Advisory Board. M. Christ-Crain reports no disclosures relevant to the manuscript. M. Arnold and M. Katan received an unconditional research grant for the measurement of MR-proANP in the CoRisk study from BRAHMS GmbH, Henningsdorf, Germany. Go to Neurology.org/N for full disclosures.

Received May 21, 2017. Accepted in final form October 30, 2017.

References

1. Whiteley W, Chong WL, Sengupta A, Sandercock P. Blood markers for the prognosis of ischemic stroke: a systematic review. Stroke 2009;40:e380–389.

2. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:2408–2416.
3. Ioannidis JP, Panagiotou OA. Comparison of effect sizes associated with biomarkers reported in highly cited individual articles and in subsequent meta-analyses. JAMA 2011;305:2200–2210.
4. Brott T, Adams HJ, Olinger C, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864–870.
5. Katan M, Fluri F, Schuetz P, et al. Midregional pro-atrial natriuretic peptide and outcome in patients with acute ischemic stroke. J Am Coll Cardiol 2010;56: 1045–1053.
6. De Marchis GM, Katan M, Weck A, et al. Copeptin and risk stratification in patients with ischemic stroke and transient ischemic attack: the CoRisk study. Int J Stroke 2013;8:214–218.
7. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. Bull World Health Organ 1980;58:113–130.
8. De Marchis GM, Katan M, Weck A, et al. Copeptin adds prognostic information after ischemic stroke: results from the CoRisk study. Neurology 2013;80:1278–1286.
9. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage: a powerful and easy-to-use predictor of 30-day mortality. Stroke 1993; 24:987–993.
10. Szabo K, Kern R, Gass A, Hirsch J, Hennerici M. Acute stroke patterns in patients with internal carotid artery disease: a diffusion-weighted magnetic resonance imaging study. Stroke 2001;32:1323–1329.
11. Goldstein L, Samsa G, Matchar D, Horner R. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. Stroke 2004;35:1941–1945.
12. Adams HJ, Bendixen B, Kappelle L, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
13. Morgenthaler NG, Struck J, Thomas B, Bergmann A. Immunoluminometric assay for the midregion of pro-atrial natriuretic peptide in human plasma. Clin Chem 2004;50: 234–236.
14. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–172; discussion 207–212.
15. Katan M, Fluri F, Morgenthaler NG, et al. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. Ann Neurol 2009;66:799–808.
16. Garcia-Berrocoso T, Giralt D, Bustamante A, et al. B-type natriuretic peptides and mortality after stroke: a systematic review and meta-analysis. Neurology 2013;81: 1976–1985.
17. Gardner DG, Vlasuk GP, Baxter JD, Fiddes JC, Lewicki JA. Identification of atrial natriuretic factor gene transcripts in the central nervous system of the rat. Proc Natl Acad Sci USA 1987;84:2175–2179.
18. Anne M, Juha K, Timo M, et al. Neurohormonal activation in ischemic stroke: effects of acute phase disturbances on long-term mortality. Curr Neurovascular Res 2007;4:170–175.
19. Nakao K, Ogawa Y, Suga S, Imura H. Molecular biology and biochemistry of the natriuretic peptide system, I: natriuretic peptides. J Hypertens 1992;10:907–912.
20. Cea LB. Natriuretic peptide family: new aspects. Curr Med Chem Cardiovasc Hematol Agents 2005;3:87–98.
21. Rosenzweig A, Seidman CE. Atrial natriuretic factor and related peptide hormones. Annu Rev Biochem 1991;60:229–255.
22. Shah RV, Truong QA, Gaggin HK, Pfannkuche J, Hartmann O, Januzzi JL Jr. Mid-regional pro-atrial natriuretic peptide and pro-adrenomedullin testing for the diagnostic and prognostic evaluation of patients with acute dyspnoea. Eur Heart J 2012; 33:2197–2205.
23. Moertl D, Berger R, Struck J, et al. Comparison of midregional pro-atrial and B-type natriuretic peptides in chronic heart failure: influencing factors, detection of left ventricular systolic dysfunction, and prediction of death. J Am Coll Cardiol 2009;53:1783–1790.
24. Kamel H, Okin PM, Longstreth WT Jr, Elkind MS, Soliman EZ. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. Future Cardiol 2015;11:323–331.
25. Hodgson-Zingman DM, Karst ML, Zingman LV, et al. Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. N Engl J Med 2008;359:158–165.
26. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429–438.

FULL-LENGTH ARTICLE NPub.org/s86roi

Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke

Gian Marco De Marchis, MD, MS,* Juliane Schneider, MD,* Anja Weck, MD, Felix Fluri, MD, Joachim Fladt, MD, Christian Foerch, MD, Beat Mueller, MD, Andreas Luft, MD, Mirjam Christ-Crain, MD, PhD, Marcel Arnold, MD,* and Mira Katan, MD, MS*

Correspondence
Dr. Katan
Mira.katan@usz.ch

Cite as: *Neurology*® 2018;90:e455-e465. doi:10.1212/WNL.0000000000004922

Study question

Can midregional proatrial natriuretic peptide (MR-proANP) levels within the first 24 hours of ischemic stroke onset improve the prediction of 90-day mortality, functional outcomes, and cardioembolic stroke etiology?

Summary answer

The MR-proANP level was an independent predictor of functional outcome, mortality, cardioembolic stroke etiology, and atrial fibrillation; however, the inclusion of MR-proANP levels improved prognostic models for mortality and atrial fibrillation only.

What is known and what this article adds

Previous single-center studies have reported that inclusion of MR-proANP levels improves the discriminatory ability of the NIH Stroke Scale (NIHSS) score for 90-day mortality. In this multicenter study, we verified the prognostic utility of MR-proANP levels regarding several outcome measures.

Participants and setting

This prospective, multicenter cohort study included 788 consecutive patients (median age 71 years; 62% men) admitted to the emergency departments of participating tertiary centers within 24 hours of acute ischemic stroke onset.

Design, size, and duration

Outcomes of interest included 90-day mortality, unfavorable outcomes (modified Rankin Scale score >2 points), diagnoses of cardioembolic stroke etiology during hospitalization, and atrial fibrillation. Blood samples for the assessment of MR-proANP levels were obtained within 24 hours of symptom onset. Regression models and the net reclassification index (NRI) were used to estimate the additive benefit of MR-proANP levels to traditional outcome predictors.

Main results and the role of chance

Inclusion of MR-proANP levels increased the discriminatory accuracy of mortality and atrial fibrillation prediction, but not of functional outcome and cardioembolic etiology. The NRI of MR-proANP for mortality was 49% (95% confidence interval [CI] 26%–78%, $p < 0.001$), and for atrial fibrillation 78% (95% CI 60%–89%, $p < 0.001$). While MR-proANP levels ≥163 pmol/L had a specificity of 56% and a sensitivity of 81% for 90-day mortality, levels ≥289 pmol/L had a specificity of 86% and sensitivity of 48% for atrial fibrillation.

Bias, confounding, and other reasons for caution

MR-proANP levels were not compared with levels of other natriuretic peptides. Residual confounding effects of associations between MR-proANP levels and other factors cannot be excluded.

Generalizability to other populations

Because of the study's multicenter design, and broad inclusion criteria, the results may be generalizable to various populations of patients with stroke.

Table Multivariable logistic regression analyses for the diagnosis of atrial fibrillation at hospital discharge WITH and WITHOUT MR-proANP

Predictors	Odds ratio	95% CI	*p* Value	Odds ratio	95% CI	*p* Value
MR-proANP, pmol/L[a]	18.35	7.94–42.45	<0.001	NA	NA	—
Age, y	1.03	1.02–1.05	<0.001	1.05	1.03–1.07	<0.001
Female sex	1.37	0.92–2.03	0.12	1.37	0.94–2.00	0.10
Hypertension	1.28	0.80–2.04	0.31	1.48	0.95–2.31	0.084
Smoking	0.52	0.28–0.95	0.032	0.51	0.28–0.91	0.023
Heart failure	1.46	0.77–2.76	0.25	1.79	0.96–3.36	0.07
Modified Charlson Index	0.92	0.78–1.05	0.17	0.96	0.83–1.11	0.56
NIHSS at admission	1.01	0.98–1.04	0.50	1.03	0.99–1.05	0.07
eGFR, mL/min/1.73 m^{2}[a]	1.51	0.86–2.63	0.15	0.71	0.43–1.17	0.17
Small lesion size on MR, DWI (1–10 mm^{3})	0.67	0.42–1.07	0.096	0.59	0.38–0.93	0.023
Pseudo-R2 Pseudo-R2			0.2047			
Pseudo-R2 without MR-proANP						0.1421

Abbreviations: DWI = diffusion weighted imaging; eGFR = estimated glomerular filtration rate; MR = magnetic resonance; MR-proANP = midregional proatrial natriuretic peptide; NA = not applicable; NIHSS = NIH Stroke Scale.
[a] Odds ratio refers to a 1-unit increase in the explanatory variable and to any 10-fold increase in MR-proANP and eGFR (log-transformed with a base of 10). All of the covariates entered in the models are listed in the table.

Study funding/potential competing interests

This study was supported by the Swiss National Science Foundation, a De Quervain research grant, Switzerland; Foundation of the Inselspital Bern; Foundation Pro Scientia et Arte, Bern; Foundation Jubiläumsstiftung der Schweizerischen Lebensversicherungs-und Rentenanstalt für Volksgesundheit und medizinische Forschung; and a Transatlantic Career Development Grant from the Foundation Leducq. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by D. Drobish, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

*These authors contributed equally to this work.

Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke

Gian Marco De Marchis, Juliane Schneider, Anja Weck, et al.

Neurology 2018;90;e455-e465 Published Online before print January 10, 2018
DOI 10.1212/WNL.0000000000004922

Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke: Association with mortality and cardioembolic etiology

Neurology® 2018;91:637. doi:10.1212/WNL.0000000000005190

In the article "Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke: Association with mortality and cardioembolic etiology" by G.M. De Marchis et al.,[1] the version published ahead of print on January 10, 2018, contained some errors. The sixth sentence of the Abstract should specify "*continuous* net reclassification index (cNRI)," and the ninth sentence should report the significance of *c*NRI of atrial fibrillation at (78%, 95% CI 60%–89%, $p < 0.001$). In the Results section, the third sentence has been changed to "The median age of the cohort was *71* (IQR 61–80) years, and 298 (*38%*) were *women*." Under the subsection "Prediction of functional outcome after 3 months," the first sentence of the second paragraph should report "(AUC change from 0.85 [95% CI 0.83–0.88] to 0.86 [95% CI 0.83–0.88], $p < 0.0071$)." The last sentence of the Results section should specify "…a *continuous* NRI of 78%." The title for table 2 should read, "Multivariate logistic *and Cox* regression analyses for 90-day functional outcome and mortality WITH and WITHOUT MR-proANP." In table 4, the number (n) and percentage (%) values were reversed from row 3 through row 12, and in table 5, row 7 should have a p value of 0.35 (for dyslipidemia), rather than 0.035 as originally published. Corrected text and tables were published in the final version on February 6, 2018. The authors regret the errors.

Reference

1. De Marchis GM, Schneider J, Weck A, et al. Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke: association with mortality and cardioembolic etiology. Neurology 2018;90:e455–e465.

Eteplirsen treatment for Duchenne muscular dystrophy: Exon skipping and dystrophin production

Neurology® 2018;91:637. doi:10.1212/WNL.0000000000005979

In the article "Eteplirsen treatment for Duchenne muscular dystrophy: Exon skipping and dystrophin production" by J.S. Charleston et al.,[1] the Acknowledgment is incomplete. It should also include "The authors also gratefully acknowledge Dr. Steven A. Moore, the University of Iowa Hospitals and Clinics Histology Laboratory, and the Iowa Wellstone Muscular Dystrophy Cooperative Research Center (NIH grant U54, NS053672) for providing frozen sections of non-dystrophic control muscle biopsies, Becker muscular dystrophy muscle biopsies, and untreated DMD biopsy samples from the PROMOVI clinical study described in this manuscript. Dr. Moore also assisted in establishing criteria for defining dystrophin positive muscle fibers." The authors regret the omission.

Reference

1. Charleston JS, Schnell FJ, Dworzak J, et al. Eteplirsen treatment for Duchenne muscular dystrophy: exon skipping and dystrophin production. Neurology 2018;90:e2146–e2154.